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Proposed Registration Decision PRD2018-10

Bacillus amyloliquefaciens strain MBI 600 and Serifel

(publié aussi en français)

1 June 2018

This document is published by the Health Canada Pest Management Regulatory Agency. For further information, please contact:

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Canada

ISSN: 1925-0878 (print)
1925-0886 (online)

Catalogue number: H113-9/2018-10E (print version)
H113-9/2018-10E-PDF (PDF version)

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Overview

Proposed Registration Decision for *Bacillus amyloliquefaciens* strain MBI 600

Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Products Act* and Regulations, is proposing registration for the sale and use of *Bacillus amyloliquefaciens* strain MBI 600 Technical and Serifel, containing the technical grade active ingredient *Bacillus amyloliquefaciens* strain MBI 600, to suppress *Botrytis cinerea* (grey mould) and *Erysiphe necator* (powdery mildew) on grapes.

The technical grade active ingredient *Bacillus amyloliquefaciens* strain MBI 600 Technical (Registration Number 29452) and the end-use product Serifel (Registration Number 30054) are currently registered for the treatment of plant growing media for the suppression of various damping-off and root diseases on various greenhouse crops (fruiting vegetables, cucurbits, and ornamentals). The detailed reviews for these products can be found in the Proposed Registration Decision PRD2009-17, *Bacillus subtilis strain MBI 600 Integral Liquid Biological Fungicide*, Registration Decision RD2010-04, *Bacillus subtilis strain MBI 600 Integral Liquid Biological Fungicide*.

An evaluation of available scientific information found that, under the approved conditions of use, the product has value and does not present an unacceptable risk to human health or the environment.

This Overview describes the key points of the evaluation, while the Science Evaluation provides detailed technical information on the human health, environmental and value assessments of *Bacillus amyloliquefaciens* strain MBI 600 Technical and Serifel.

What Does Health Canada Consider When Making a Registration Decision?

The key objective of the *Pest Control Products Act* is to prevent unacceptable risks to human health and the environment from the use of pest control products. Health or environmental risk is considered acceptable[1] if there is reasonable certainty that no harm to human health, future generations or the environment will result from use or exposure to the product under its proposed conditions of registration. The Act also requires that products have value[2] when used according to the label directions. Conditions of registration may include special precautionary measures on the product label to further reduce risk.

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1 "Acceptable risks" as defined by subsection 2(2) of the *Pest Control Products Act*.

2 "Value" as defined by subsection 2(1) of the *Pest Control Products Act*: "... the product's actual or potential contribution to pest management, taking into account its conditions or proposed conditions of registration, and includes the product's (*a*) efficacy; (*b*) effect on host organisms in connection with which it is intended to be used; and (*c*) health, safety and environmental benefits and social and economic impact."

To reach its decisions, the PMRA applies modern, rigorous risk-assessment methods and policies. These methods consider the unique characteristics of sensitive subpopulations in humans (for example, children) as well as organisms in the environment. These methods and policies also consider the nature of the effects observed and the uncertainties when predicting the impact of pesticides. For more information on how the PMRA regulates pesticides, the assessment process and risk-reduction programs, please visit the Pesticides and Pest Management section of the Canada.ca website.

Before making a final registration decision on *Bacillus amyloliquefaciens* strain MBI 600 Technical and Serifel, the PMRA will consider any comments received from the public in response to this consultation document.[3] The PMRA will then publish a Registration Decision[4] on *Bacillus amyloliquefaciens* strain MBI 600 Technical and Serifel, which will include the decision, the reasons for it, a summary of comments received on the proposed final registration decision and the PMRA's response to these comments.

For more details on the information presented in this Overview, please refer to the Science Evaluation of this consultation document.

What Is *Bacillus amyloliquefaciens* strain MBI 600?

Bacillus amyloliquefaciens strain MBI 600 is the active ingredient in Serifel, a biological fungicide currently registered in Canada for the treatment of plant growing media such as soil and peat moss-based mixtures to suppress seedling and root diseases caused by various fungal pathogens on greenhouse vegetables and ornamentals. *Bacillus amyloliquefaciens* strain MBI 600 is being proposed for use as a foliar spray on grapes.

Health Considerations

Can Approved Uses of *Bacillus amyloliquefaciens* strain MBI 600 Affect Human Health?

***Bacillus amyloliquefaciens* strain MBI 600 is unlikely to affect your health when Serifel is used according to the label directions.**

Potential exposure to *Bacillus amyloliquefaciens* strain MBI 600 may occur when handling and applying Serifel, and when ingesting treated produce. When assessing health risks, several key factors are considered:

- the microorganism's biological properties (e.g., infection cycle);
- reports of any adverse incidents;
- its potential to cause disease or toxicity as determined in toxicological studies; and
- the level to which people may be exposed relative to exposures already encountered in nature to other isolates of this microorganism.

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3 "Consultation statement" as required by subsection 28(2) of the *Pest Control Products Act*.

4 "Decision statement" as required by subsection 28(5) of the *Pest Control Products Act*.

The levels used to assess risks are established to protect the most sensitive human population (for example, children and nursing mothers). As such, sex and gender are taken into account in the risk assessment. Only uses that are determined as having no health risks of concern are considered acceptable for registration.

Studies in laboratory animals describe potential health effects from large doses of exposure to a microorganism and identify any potential pathogenicity, infectivity and toxicity concerns. When *Bacillus amyloliquefaciens* strain MBI 600 was tested on laboratory animals, there was no sign that it caused any toxicity from oral or dermal exposures. Slight toxicity was observed via the pulmonary route. There was no sign that *Bacillus amyloliquefaciens* strain MBI 600 caused any disease.

Residues in Water and Food

Dietary risks from food and water are not of concern.

Residues of *Bacillus amyloliquefaciens* strain MBI 600 on treated food crops are possible at the time of harvest. While *Bacillus amyloliquefaciens* and its close relative, *Bacillus subtilis*, are abundant in nature, only a few cases involving foodborne illness in people have been reported and only with isolates that are able to produce a toxin which is not known to be produced by *Bacillus amyloliquefaciens* strain MBI 600. Since its registration on food crops in 1994 in the United States and in 2007 in Canada, there have been no foodborne illnesses reported for *Bacillus amyloliquefaciens* strain MBI 600. Moreover, no signs of infectivity or toxicity were observed when *Bacillus amyloliquefaciens* strain MBI 600 was tested on laboratory animals. In addition, the likelihood of residues of *Bacillus amyloliquefaciens* strain MBI 600 contaminating drinking water supplies from the proposed spray application of Serifel on food crops is low. Consequently, dietary risks are also low and not a health concern.

Risks in Residential and Other Non-Occupational Environments

Estimated risk for non-occupational exposure is not of concern.

Serifel is proposed only for use on agricultural field crops, and the product label includes mitigation measures to minimize bystander exposure. Consequently, it is unlikely that adults, youths and toddlers will be exposed to *Bacillus amyloliquefaciens* strain MBI 600. Even in the event of exposure, risk to the general population is not a concern since there were no signs that it caused any significant toxicity or disease in studies on laboratory animals.

Occupational Risks From Handling Serifel

Occupational risks are not of concern when Serifel is used according to label directions, which include protective measures.

Workers handling Serifel can come into direct contact with *Bacillus amyloliquefaciens* strain MBI 600 on the skin, in the eyes or by inhalation. For this reason, the product label will specify that workers must wear personal protective equipment, including waterproof gloves, long-sleeved shirts, long pants, a mist and dust filtering mask or respirator, eye goggles and shoes

with socks. In addition, all unprotected workers are restricted from entering areas during application and for 4 hours following application or until all sprays have dried.

Environmental Considerations

What Happens When *Bacillus amyloliquefaciens* strain MBI 600 Is Introduced into the Environment?

Environmental risks are not of concern.

Information on the environmental fate of *Bacillus amyloliquefaciens* strain MBI 600 suggests that, as a soil microorganism, it is likely to readily survive after applications of Serifel to agricultural field crops, but that over time its population should return to naturally sustained levels.

There are no published reports of disease associated with *Bacillus amyloliquefaciens* in birds, earthworms, bees, aquatic invertebrates, fish, algae, and aquatic plants. Also, the registrant-submitted studies designed to examine the effects of *Bacillus amyloliquefaciens* strain MBI 600 to bees, aquatic invertebrates and aquatic plants reported no adverse effects.

Based on a critical review of registrant-submitted studies and information from public sources, no significant effects to birds, wild mammals, fish, terrestrial and aquatic arthropods, terrestrial and aquatic non-arthropod invertebrates and plants are expected when Serifel is applied according to directions on the label.

Value Considerations

What Is the Value of Serifel?

This registration will offer a new method of application for the biological fungicide Serifel that will allow for the suppression of two major diseases in grape production: grey mould and powdery mildew.

Serifel is currently registered for direct application to plant-growing media to suppress seedling and root diseases caused by certain fungi and oomycetes. This registration will allow grape producers to apply Serifel directly onto foliage, bloom, and fruit to suppress grey mould and powdery mildew, two diseases with potentially severe economic impact on Canadian grape production. This new major use for Serifel will also provide growers with an additional option in terms of biological active ingredients and non-conventional end-use products to manage grape diseases.

Measures to Minimize Risk

Labels of registered pesticide products include specific instructions for use. Directions include risk-reduction measures to protect human and environmental health. These directions must be followed by law.

The key risk-reduction measures being proposed on the labels of *Bacillus amyloliquefaciens* strain MBI 600 Technical and Serifel to address the potential risks identified in this assessment are as follows.

Key Risk-Reduction Measures

Human Health

All microorganisms, including *Bacillus amyloliquefaciens* strain MBI 600, contain substances that are potential sensitizers and thus, respiratory and dermal sensitivity may possibly develop in individuals exposed to potentially large quantities of *Bacillus amyloliquefaciens* strain MBI 600. In turn, workers handling or applying Serifel must wear waterproof gloves, long-sleeved shirt, long pants, eye goggles, a mist and dust filtering mask or respirator, and shoes with socks. Furthermore, all unprotected workers are restricted from entering treated areas during application and for 4 hours following application or until sprays have dried.

A standard drift statement is also required on the Serifel label to minimize the potential for drift to areas of human habitation or areas of human activity such as houses, cottages, schools and recreational areas.

Environment

The end-use product label will include environmental precaution statements to limit drift and minimize runoff and contamination of aquatic systems from the use of Serifel.

Next Steps

Before making a final registration decision on *Bacillus amyloliquefaciens* strain MBI 600 Technical and Serifel, the PMRA will consider any comments received from the public in response to this consultation document. The PMRA will accept written comments on this proposal up to 45 days from the date of publication of this document. Please forward all comments to Publications (contact information on the cover page of this document). The PMRA will then publish a Registration Decision, which will include its decision, the reasons for it, a summary of comments received on the proposed final decision and the Agency's response to these comments.

Other Information

When the PMRA makes its registration decision, it will publish a Registration Decision on *Bacillus amyloliquefaciens* strain MBI 600 Technical and Serifel (based on the Science Evaluation of this consultation document). In addition, the test data referenced in this consultation document will be available for public inspection, upon application, in the PMRA's Reading Room (located in Ottawa).

Science Evaluation

***Bacillus amyloliquefaciens* strain MBI 600**

1.0 The Active Ingredient, Its Properties and Uses

1.1 Identity of the Active Ingredient

Active ingredient	Viable spores of *Bacillus amyloliquefaciens* strain MBI 600
Function	Biological Fungicide – To suppress *Botrytis cinerea* and *Erysiphe necator* on grapes
Binomial name	*Bacillus amyloliquefaciens* strain MBI 600
Taxonomic designation	
Kingdom	Eubacteria
Phylum	Firmicutes
Class	Bacilli
Order	Bacillales
Family	Bacillaceae
Genus	*Bacillus*
Species	*amyloliquefaciens* (formerly *subtilis*)
Strain	MBI 600

(www.ncbi.nlm.nih.gov/Taxonomy/taxonomyhome.html)

Patent Status information	Canadian Patents: i. 1324099 Issued: 9 November 1993 Expiration: 9 November 2010 ii. 1337935 Issued: 16 January 1996 Expiration: 16 January 2013
Minimum purity of active	Technical Grade Active Ingredient: minimum of 5.0×10^{11} viable spores/g End-use Product: minimum of 5.5×10^{10} viable spores/g

Identity of relevant impurities of toxicological, environmental and/or significance.	The technical grade active ingredient does not contain any impurities or microcontaminants known to be Toxic Substances Management Policy (TSMP) Track 1 substances. In public scientific literature, *Bacillus subtilis* has been reported to produce small antibiotic peptides and peptidolipids that are predominantly active against Gram-positive bacteria, but also against Gram-negative bacteria, yeast and fungi. These include intracellular peptidolipids (mycosubtilin), extracellular cyclic peptidolipids (*Aspergillus* factor, bacillomycin A/B/D/F/L/R/S, eumycin, fengycin, iturin A and toximycin) and extracellular cyclic peptides (chaetomacin, fungistatin, mycobacillin and *Rhizoctonia* factor). Hemolytic activity has been reported for some peptidolipids. Strain MBI 600 also produces a 63 kDa antibiotic protein with demonstrated activities against Gram-positive bacteria and fungi, but no mammalian toxicity has been reported. The product must meet microbiological contaminants release standards.

1.2 Physical and Chemical Properties of the Active Ingredients and End-use Product

Technical Product—*Bacillus amyloliquefaciens* strain MBI 600 Technical

Property	Result
Colour	Light cream
Physical State	Fine dry powder
Odour	Musty
Corrosion Characteristics	Non-corrosive
pH	6.0 (1% aqueous solution)
Density	0.28 g/cm^3

End-use Product—Serifel

Property	Result
Colour	Beige-white
Physical State	Solid
Odour	Musty
Corrosion Characteristics	Non-corrosive
Suspendibility	Soluble in water
Density	2.0 – 2.3 g/cm^3

1.3 Directions for Use

For suppression of grey mould and powdery mildew on grapes under low to moderate disease pressure, Serifel may be applied by spraying on all aerial parts of the grapevine at rates ranging from 0.25 to 0.5 kg of product per hectare. Applications should begin when conditions are conducive to disease development, prior to the appearance of symptoms. The product can then be re-applied on intervals of five to ten days until protection is no longer required.

1.4 Mode of Action

The active ingredient in the biological fungicide Serifel, *Bacillus amyloliquefaciens* strain MBI 600, is classified as a Group 44 fungicide by the Fungicide Resistance Action Committee (FRAC). This naturally occurring bacteria suppresses plant diseases by preventing growth of pathogenic fungi through displacement and direct antagonistic action.

2.0 Methods of Analysis

2.1 Methods for Identification of the Microorganisms

The microbial pest control agent (MPCA) was initially registered as *B. subtilis* strain MBI 600. A taxonomic analysis has since been provided that supports a re-classification of the species designation to *amyloliquefaciens*. A revised method of identification was also provided.

The method employed to identify *B. amyloliquefaciens* strain MBI 600 involves the DNA sequence analysis of the V3 region of the 16s rRNA gene for the presence of *RsaI* restriction sites (GATC) at nucleotides 473 and 492. The presence of these *RsaI* sites in that region is specific to the *B. amyloliquefaciens* species. Additionally, a full DNA sequence of the MBI 600 strain is available should it be required.

2.2 Methods for Establishment of Purity of Seed Stock

Acceptable methods for establishment of purity of seed stock were fully described for the MPCA in support of the initial registration decisions. For additional information on these methods see PRD2009-17, *Bacillus subtilis strain MBI 600 Integral Liquid Biological Fungicide*.

2.3 Methods to Define the Content of the Microorganism in the Manufactured Material Used for the Production of Formulated Products

The guarantees of Serifel and *Bacillus amyloliquefaciens* strain MBI 600 Technical are expressed in units of viable spores per gram. Representative data on batches of the technical grade active ingredient and end-use product were previously submitted by the registrant.

2.4 Methods to Determine and Quantify Residues (Viable or Non-viable) of the Active Microorganism and Relevant Metabolites

Acceptable methods are available to enumerate the MPCA and to distinguish between other species of *Bacillus* and other strains of *B. amyloliquefaciens*.

2.5 Methods for Determination of Relevant Impurities in the Manufactured Material

Acceptable methods for the determination of relevant impurities in the manufactured material were described in previous registration decisions. For additional information on the quality assurance procedures, see PRD2009-17, *Bacillus subtilis strain MBI 600 Integral Liquid Biological Fungicide*.

The absence of human pathogens and below-threshold levels of contaminating microorganisms were shown in the microbial screening of batches of *Bacillus amyloliquefaciens* strain MBI 600 Technical and Serifel using standard methods for detecting and enumerating microbial contaminants of concern. In addition, all batches of *Bacillus amyloliquefaciens* strain MBI 600 Technical must conform to the limits set out in the Organization for Economic Co-operation and Development issue paper on microbial contaminants for microbial pest control products [ENV/JM/MONO(2011)43].

2.6 Methods to Determine Storage Stability, Shelf-life of the Microorganism

Storage stability data were previously submitted by the registrant for Serifel. Results support a storage period of 16 months at 25°C.

3.0 Impact on Human and Animal Health

3.1 Toxicity and Infectivity Summary

3.1.1 Testing

No new human health and safety data were submitted or required for the proposed use pattern. The PMRA instead relied on previous registrant-submitted data and open literature sources evaluated in support of initial registration to assess human health risks associated with the proposed new use of *B. amyloliquefaciens* strain MBI 600 Technical and Serifel. Toxicity and infectivity information related to *B. amyloliquefaciens* strain MBI 600 can be found in PRD2009-17, *Bacillus subtilis strain MBI 600 Integral Liquid Biological Fungicide*.

3.1.2 Additional Information

No new additional information was submitted by the registrant to address human health and safety requirements for *B. amyloliquefaciens* strain MBI 600 Technical and Serifel.

3.1.3 Incident Reports Related to Human and Animal Health

As of 6 November 2017, no human, domestic animal or environment incident reports involving *B. amyloliquefaciens* have been submitted to the PMRA. However, the PMRA received one human incident involving the active *Bacillus subtilis*. In this incident, a person reported minor symptoms of rash and cough following product application. Based on the low severity of the reported incident, no additional risk mitigation measures are recommended.

3.1.4 Hazard Analysis

Based on a review of previous registrant-submitted data and open scientific literature, *Bacillus amyloliquefaciens* strain MBI 600 Technical was of low toxicity when administered via oral and dermal exposure routes, but slight toxicity was observed via the pulmonary route. *Bacillus amyloliquefaciens* strain MBI 600, is not pathogenic or infective via the oral, pulmonary and intravenous injection exposure routes. Furthermore, *Bacillus amyloliquefaciens* strain MBI 600 Technical is minimally irritating to the eyes and is considered to be minimally irritating to the

skin and is considered to be a potential sensitizer. Consequently, the hazard statement "POTENTIAL SENSITIZER" must appear on the principal display panel of the *Bacillus amyloliquefaciens* strain MBI 600 Technical label, and the following precautionary statement must appear on the label's secondary display panel: "May cause sensitization. Avoid contact with eyes, skin and clothing. Avoid breathing dust."

Serifel is considered to be of low toxicity via the oral, pulmonary and dermal routes, and is considered to be minimally irritating to the skin and eyes and a potential sensitizer. Therefore, the hazard statement "POTENTIAL SENSITIZER" must appear on the principal display panel of the Serifel label and the following precautionary statement must appear on the label's secondary display panel: "May cause sensitization. Avoid contact with eyes, skin and clothing. Avoid breathing dust."

Higher tier subchronic and chronic toxicity studies were not required because there are no indications of infectivity, toxicity or pathogenicity in the test animals treated in the Tier I acute oral, pulmonary and intravenous toxicity/infectivity tests.

3.2 Occupational, Residential and Bystander Risk Assessment

3.2.1 Occupational Exposure and Risk

When handled according to the label instructions, the potential for dermal, eye and inhalation exposure for applicators, mixer/loaders, and handlers exists, with primary exposure routes being dermal and inhalation. Since unbroken skin is a natural barrier to microbial invasion of the human body, dermal absorption could occur only if the skin were cut, if the microbe was a pathogen equipped with mechanisms for entry through or infection of the skin, or if metabolites were produced that could be dermally absorbed. *Bacillus amyloliquefaciens* has not been identified as a dermal wound pathogen and there is no indication that it could penetrate intact skin of healthy individuals. Furthermore, toxicity testing with the technical grade active ingredients showed no toxicity via the oral and dermal routes, and it was minimally irritating to the skin and eyes. Also, testing with the technical grade active ingredient showed no signs of infectivity or pathogenicity via the oral, pulmonary (intratracheal) or intravenous injection routes. The risk of toxicity exists in individuals exposed to large quantities of spores of *B. amyloliquefaciens* strain MBI 600 by inhalation. In addition, the PMRA assumes that all microorganisms contain substances that can elicit positive hypersensitivity reactions, regardless of the outcome of sensitization testing.

Risk mitigation measures, such as personal protective equipment, including waterproof gloves, long-sleeved shirts, long pants, eye goggles, a NIOSH-approved dust or mist filtering mask or respirator, and shoes with socks are required to minimize exposure and protect commercial applicators, mixer/loaders, and handlers that are likely to be exposed. In addition, all unprotected workers and users are prohibited from entering treated areas where Serifel has been applied for 4 hours or until the sprays have dried.

Label warnings, restrictions and risk mitigation measures are adequate to protect users of Serifel and no occupational risks of concern are anticipated for this product.

3.2.2 Residential and Bystander Exposure and Risk

There is a potential for bystander exposure to spray drift from applications to outdoor field crops. For bystanders, inhalation exposure is expected to be much less than that of handlers and mixer/loaders.

Overall, the PMRA does not expect that residential and bystander exposures will pose a health risk of concern on the basis of the low toxicity profile for Serifel, the low infectivity/pathogenicity profile for *Bacillus amyloliquefaciens* strain MBI 600 Technical, and the expectation that precautionary label statements will be followed by commercial applicators in the use of Serifel. As well, *B. amyloliquefaciens* is a species that is common in the environment and the use of Serifel is not expected to cause sustained increases in exposure to bystanders beyond natural levels. Consequently, the health risk to infants and children is expected to be low and not of concern.

3.3 Dietary Exposure and Risk Assessment

3.3.1 Food

While the proposed use pattern may result in dietary exposure with possible residues in or on agricultural commodities, dietary risk is expected to be low and not of concern to the general population and sensitive subpopulations such as infants and children, or to animals because *B. amyloliquefaciens* strain MBI 600 demonstrated no pathogenicity or infectivity in Tier I acute oral, pulmonary (intratracheal) and intravenous injection studies; and no oral toxicity in the acute toxicity study. Furthermore, higher-tier subchronic and chronic toxicity studies were not required because of the anticipated low toxicity and lack of infectivity or pathogenicity associated with the MPCA.

3.3.2 Drinking Water

Health risks are not expected from exposure to *B. amyloliquefaciens* strain MBI 600 Technical via drinking water because exposure will be low from operational applications and because there were no harmful effects observed in Tier I acute oral toxicity testing and infectivity testing. The Serifel label instructs users not to contaminate irrigation or drinking water supplies or aquatic habitats through equipment cleaning or waste disposal. Users are also to minimize effluent or runoff from greenhouses and runoff from outdoor applications to enter lakes, streams, ponds or other bodies of water. Furthermore, municipal treatment of drinking water is expected to reduce the transfer of residues to drinking water.

3.3.3 Acute and Chronic Dietary Risks for Sensitive Subpopulations

Calculations of acute reference doses (ARfDs) and acceptable daily intakes (ADIs) are not usually possible for predicting acute and long-term effects of microbial agents in the general population or to potentially sensitive subpopulations, particularly infants and children. The single (maximum hazard) dose approach to testing MPCAs is sufficient for conducting a reasonable general assessment of risk if no significant adverse effects (in other words, no acute toxicity, infectivity or pathogenicity endpoints of concern) are noted in acute toxicity and infectivity tests.

Based on all the available information and hazard data, the PMRA concludes that *B. amyloliquefaciens* strain MBI 600 Technical is of low oral toxicity, is not pathogenic or infective to mammals, and that infants and children are likely to be no more sensitive to the MPCAs than the general population. Thus there are no threshold effects of concern and, as a result, there is no need to require definitive (multiple dose) testing or apply uncertainty factors to account for intra- and interspecies variability, safety factors or margins of exposure. Further factoring of consumption patterns among infants and children, special susceptibility in these subpopulations to the effects of the MPCA, including neurological effects from pre- or post-natal exposures, and cumulative effects on infants and children of the MPCA and other registered microorganisms that have a common mechanism of toxicity, does not apply to this MPCA. As a result, the Agency has not used a margin of exposure (safety) approach to assess the risks of *B. amyloliquefaciens* strain MBI 600 to human health.

3.3.4 Aggregate Exposure and Risk

Based on the toxicity and infectivity test data previously submitted and other relevant information in the PMRA's files, there is reasonable certainty that no harm will result from aggregate exposure of residues of *B. amyloliquefaciens* strain MBI 600 to the general Canadian population, including infants and children, when Serifel is used as labelled. This includes all anticipated dietary (food and drinking water) exposures and all other non-occupational exposures (dermal and inhalation) for which there is reliable information. Dermal and inhalation exposure to the general public will be low since the product is not allowed for use on turf, residential or recreational areas. Furthermore, the label will include mitigation measures to reduce spray drift and few adverse effects from exposure to other strains of *B. amyloliquefaciens* encountered in the environment have been reported in the public literature. Even if there is an increase in exposure to *B. amyloliquefaciens* strain MBI 600 from the use of Serifel, there should not be any increase in potential human health risk.

3.3.5 Maximum Residue Limits

As part of the assessment process prior to the registration of a pesticide, Health Canada must determine whether the consumption of the maximum amount of residues, that are expected to remain on food products when a pesticide is used according to label directions, will not be a concern to human health. This maximum amount of residues expected is then legally specified as a maximum residue limit (MRL) under the *Pest Control Products Act* for the purposes of the adulteration provision of the *Food and Drugs Act*. Health Canada specifies science-based MRLs to ensure the food Canadians eat is safe.

Residues of *B. amyloliquefaciens* strain MBI 600 on treated food crops, at the time of harvest, are anticipated following foliar applications to grapes. Consequently, the PMRA has applied a hazard-based approach for determining whether an MRL is required for this microorganism. Although the United States Food and Drug Administration has noted that some strains of *B. subtilis* have been isolated from food implicated in food poisoning, these strains demonstrated the ability to produce a highly heat-stable toxin that was not reported in *B. amyloliquefaciens* strain MBI 600. No such illnesses were reported for this microorganism in the United States where it has been registered for use on crops since 1994, or in Canada where it has been

registered since 2007. The risks anticipated for dietary exposure are considered low based on the low toxicity profile demonstrated in the test animals in the Tier I acute oral, pulmonary (intratracheal), toxicity/infectivity and intravenous injection infectivity studies. In addition, the likelihood of residues contaminating drinking water supplies is negligible to non-existent. Therefore, the PMRA has determined that specification of an MRL under the *Pest Control Products Act* is not required for *B. amyloliquefaciens* strain MBI 600.

3.4 Cumulative Assessment

The *Pest Control Products Act* requires that the PMRA consider the cumulative exposure to pesticides with a common mechanism of toxicity. In its assessment of common mechanism of toxicity, the PMRA considers both the taxonomy of MPCAs and the production of any potentially toxic metabolites. For the current evaluation, the PMRA has determined that *B. amyloliquefaciens* strain MBI 600 shares a common mechanism of toxicity with the registered MPCAs *B. amyloliquefaciens* strain D747, *B. subtilis* strain QST 713, *B. subtilis* strain GB03, and *B. subtilis* var. *amyloliquefaciens* strain FZB24. The potential health risks from cumulative exposure of *B. amyloliquefaciens* strain MBI 600 and these other registered MPCAs are not of concern when used as labelled given their low toxicity and pathogenicity.

4.0 Impact on the Environment

4.1 Fate and Behaviour in the Environment

Environmental fate data (Tier II/III) are not normally required at Tier I, and are only triggered if significant toxicological effects in non-target organisms are noted in Tier I testing.

Environmental fate and behaviour information related to *Bacillus amyloliquefaciens* strain MBI 600 was addressed in the initial registration of this MPCA and can be found in PRD2009-17, *Bacillus subtilis strain MBI 600 Integral Liquid Biological Fungicide*.

Therefore, while no new studies were submitted to address the environmental fate and behaviour of *B. amyloliquefaciens* strain MBI 600, the field use of Serifel is expected to only temporarily increase populations of this soil microbe in environmental matrices, and levels of *B. amyloliquefaciens* strain MBI 600 are expected to return to sustained background levels over time.

4.2 Effects on Non-Target Species

The PMRA has a four-tiered approach to environmental testing of microbial pesticides. Tier I studies consist of acute studies on up to seven broad taxonomic groups of non-target organisms exposed to a maximum hazard or Maximum Challenge Concentration (MCC) of the MPCA. The MCC is generally derived from the amount of the MPCA, or its toxin, expected to be available following application at the maximum recommended label rate multiplied by a safety factor. Tier II studies consist of environmental fate (persistence and dispersal) studies as well as additional acute toxicity testing of MPCAs.

Tier III studies consist of chronic toxicity studies (i.e., life cycle studies) as well as definitive toxicity testing (e.g., LC_{50}, LD_{50}). Tier IV studies consist of experimental field studies on toxicity and fate, and are required to determine whether adverse effects are realized under actual use conditions.

The type of environmental risk assessment conducted on MPCAs varies depending on the tier level that was triggered during testing. For many MPCAs, Tier I studies are sufficient to conduct environmental risk assessments. Tier I studies are designed to represent "worst-case" scenarios where the exposure conditions greatly exceed the expected environmental concentrations. The absence of adverse effects in Tier I studies are interpreted as minimal risk to the group of non-target organisms. However, higher tiered studies will be triggered if significant adverse effects on non-target organisms are identified in Tier I studies. These studies provide additional information that allows the PMRA to refine the environmental risk assessments. In the absence of adequate environmental fate and/or field studies, a screening level risk assessment can be performed to determine if the MPCA is likely to pose a risk to a group of non-target organisms.

The screening level risk assessment uses simple methods, conservative exposure scenarios (e.g., direct application at a maximum application rate) and sensitive toxicity endpoints. A risk quotient (RQ) is calculated by dividing the exposure estimate by an appropriate toxicity value (RQ = exposure/toxicity), and the risk quotient is then compared to the level of concern (LOC).

If the screening level risk quotient is below the level of concern, the risk is considered negligible and no further risk characterization is necessary. If the screening level risk quotient is equal to or greater than the level of concern, then a refined risk assessment is performed to further characterize the risk. A refined assessment takes into consideration more realistic exposure scenarios (environmental fate and/or field testing results). Refinements to the risk assessment may continue until the risk is adequately characterized or no further refinements are possible.

4.2.1 Effects on Terrestrial Organisms

To support the proposed use expansion to outdoor food crops, the registrant submitted a honey bee toxicity study. The PMRA also considered previously submitted bird, arthropod, bee, and plant studies and scientific rationales to address other non-target species hazards of *B. amyloliquefaciens* strain MBI 600.

In a 48-hour contact, toxicity study, honeybees (*Apis mellifera*) were exposed to *B. amyloliquefaciens* strain MBI 600 applied dorsally in suspension with deionized water at a dose of 100 µg/bee (equivalent to a measured dose of 4.4×10^8 CFU/bee). No treatment related signs of toxicity were noted in the test group bees. The 48-hour contact LC_{50} was > 100 µg/bee. The NOEC value, based on mortality/sublethal effects, was 100 µg/bee.

Previously assessed waivers for avian pulmonary testing, wild mammals, and non-arthropod invertebrates toxicity testing were deemed acceptable to address the remaining environmental toxicological requirements. The rationales were based on the ubiquitous nature of members of the *B. subtilis* group in both soil and water; the toxicity profile of *B. amyloliquefaciens* strain MBI 600 from laboratory animal studies; and a review of published literature which indicated

only a few reports of adverse effects to terrestrial non-target organisms from natural populations of *B. amyloliquefaciens*.

Previously assessed terrestrial non-target organism information related to *B. amyloliquefaciens* strain MBI 600 can be found in PRD2009-17, *Bacillus subtilis strain MBI 600 Integral Liquid Biological Fungicide*.

Based on all the available information on the effects of *B. amyloliquefaciens* strain MBI 600 to terrestrial non-target organisms, there is reasonable certainty that no harm will be caused to birds, wild mammals, arthropods, non-arthropod invertebrates, plants or to other non-target microorganisms from the proposed use of Serifel as a foliar spray on grapes.

4.2.2 Effects on Aquatic Organisms

To support the proposed use expansion, toxicity studies on daphnids and green algae were submitted by the registrant. The PMRA also considered a previously submitted freshwater fish study and scientific rationales to address the hazards of *B. amyloliquefaciens* strain MBI 600 to aquatic non-target organisms.

In a 48-hour toxicity study 20 daphnids (*Daphnia magna*) were exposed to 100 mg/L of *Bacillus amyloliquefaciens* strain MBI 600 (1.06×10^{12} viable spores per gram) under static conditions in moderately hard synthetic freshwater. Daphnids were observed for mobility and mortality. Ninety percent of daphnids in the test group were mobile at 48 hours. There were no mortalities or signs of toxicity. The 48-hour LC_{50} was > 100mg/L. The 48-hour EC_{50} and 48-hour NOEC values, based on mortality/sublethal effects, were > 100 mg/L and 100 mg/L, respectively.

The effect of *B. amyloliquefaciens* strain MBI 600 on the freshwater green algae (*Pseudokirchneriella subcapitata*), was studied at nominal concentrations of 100 mg/mL (5.8×10^8 CFU/mL [measured at 0 hours]) under static conditions. The 72-hour EC_{50} of *B. amyloliquefaciens* strain MBI 600 was determined to be greater than 100 mg/L (5.8×10^8 CFU/mL [measured]). There were no treatment related effects observed.

Additional aquatic non-target organism information related to *B. amyloliquefaciens* strain MBI 600 can be found in PRD2009-17, *Bacillus subtilis strain MBI 600 Integral Liquid Biological Fungicide*.

Based on all the available information on the effects of *B. amyloliquefaciens* strain MBI 600 to aquatic non-target organisms, there is reasonable certainty that no harm will be caused to fish, aquatic arthropods, aquatic non-arthropod invertebrates or aquatic plants from the proposed use of Serifel as a foliar spray on grapes.

4.3 Incident Reports related to the Environment

As of 6 November 2017, no environment incidents involving the active *B. subtilis* or *B. amyloliquefaciens* were reported to the PMRA.

5.0 Value

The efficacy of Serifel against grey mould and powdery mildew on grapes was demonstrated by ten small-scale field trials conducted in the United States and Europe under conditions similar to those in Canadian grape growing regions. Results demonstrated levels of efficacy for Serifel that were consistent with claims of disease suppression under conditions of low to moderate disease pressure.

Numerous conventional and several non-conventional and/or biological fungicides are currently registered to control or suppress both grey mould and powdery mildew on grapes. Many of the conventional end-use products registered in Canada against these diseases are combinations of two different active ingredients. Other products containing different species or strains of *Bacillus* are also registered in Canada for this use.

Based on its mode of action, Serifel is unlikely to present a risk of stimulating resistance in the target grape pathogens. Under conditions of low disease pressure, the use of Serifel may reduce the number of required applications of conventional active ingredients, some of which do present high risk of disease resistance. Consequently, by integrating Serifel into conventional fungicide spray programs, development of resistance in these major grape diseases may be prevented or slowed.

No indication of phytotoxicity was observed in any of the ten Serifel trials conducted on grapes that were submitted in support of this registration. Based on these results and the nature of the active ingredient, Serifel, when used according to label directions, is not expected to result in any non-safety adverse effects on grapes.

6.0 Pest Control Product Policy Considerations

6.1 Toxic Substances Management Policy Considerations

The Toxic Substances Management Policy (TSMP) is a federal government policy developed to provide direction on the management of substances of concern that are released into the environment. The TSMP calls for the virtual elimination of Track 1 substances [those that meet all four criteria outlined in the policy, i.e., persistent (in air, soil, water and/or sediment), bio-accumulative, primarily a result of human activity and toxic as defined by the *Canadian Environmental Protection Act*].

Bacillus amyloliquefaciens strain MBI 600 Technical and Serifel were assessed in accordance with the PMRA Regulatory Directive DIR99-03.[5]

- *Bacillus amyloliquefaciens* strain MBI 600 Technical does not meet the Track 1 criteria because the active ingredient is a biological organism and hence is not subject to the

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[5] Regulatory Directive DIR99-03, *The Pest Management Regulatory Agency's Strategy for Implementing the Toxic Substances Management Policy*

criteria used to define persistence, bioaccumulation and toxicity properties of chemical control products.

- There are also no formulants, contaminants or impurities present in the end-use product that would meet the TSMP Track-1 criteria.

6.2 Formulants and Contaminants of Health Concern

During the review process, contaminants in the technical and formulants and contaminants in the end-use products are compared against the *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern* maintained in the *Canada Gazette*.[6] The list is used as described in the PMRA Notice of Intent NOI2005-01[7] and is based on existing policies and regulations including: DIR99-03; and DIR2006-02[8] and taking into consideration the Ozone-depleting Substance Regulations, 1998, of the *Canadian Environmental Protection Act* (substances designated under the Montreal Protocol). The PMRA has reached the following conclusions:

- The technical grade active ingredient, *Bacillus amyloliquefaciens* strain MBI 600 Technical, does not contain formulants of health or environmental concern as identified in the *Canada Gazette*, Part II, Volume 139, Number 24, pages 2641-2643: *List of Pest Control Product Formulants of Health or Environmental Concern*.

- The end-use product, Serifel, does not contain formulants of health or environmental concern as identified in the *Canada Gazette*, Part II, Volume 139, Number 24, pages 2641-2643: *List of Pest Control Product Formulants of Health or Environmental Concern*.

The use of formulants in registered pest control products is assessed on an ongoing basis through PMRA formulant initiatives and DIR2006–02.

7.0 Summary

7.1 Methods for Analysis of the Microorganism as Manufactured

The product characterization data, including data and information previously submitted, for *B. amyloliquefaciens* strain MBI 600 Technical and Serifel were adequate to assess their potential human health and environmental risks. The technical grade active ingredient was fully

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6 *Canada Gazette*, Part II, Volume 139, Number 24, SI/2005-11-30) pages 2641-2643: *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern* and in the order amending this list in the *Canada Gazette*, Part II, Volume 142, Number 13, SI/2008-67 (2008-06-25) pages 1611-1613: *Part 1 Formulants of Health or Environmental Concern, Part 2 Formulants of Health or Environmental Concern that are Allergens Known to Cause Anaphylactic-Type Reactions and Part 3 Contaminants of Health or Environmental Concern.*

7 Notice of Intent NOI2005-01, *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern* under the New *Pest Control Products Act*.

8 Regulatory Directive DIR2006-02, *Formulants Policy and Implementation Guidance Document.*

characterized and the specifications of the end-use product were supported by the analyses of a sufficient number of batches. All batches of *B. amyloliquefaciens* strain MBI 600 Technical must conform to the limits set out in the Organization for Economic Co-operation and Development issue paper on microbial contaminants for microbial pest control products [ENV/JM/MONO(2011)43]. Storage stability data previously submitted were sufficient to support a shelf life for Serifel of 16 months at 25°C.

7.2 Human Health and Safety

The scientific waiver rationales and acute toxicity and infectivity studies previously submitted in support of *B. amyloliquefaciens* strain MBI 600 Technical and Serifel were determined to be sufficiently complete to permit a decision on registration.

Based on all the available information, *B. amyloliquefaciens* strain MBI 600 Technical is of low toxicity by the oral, dermal and intravenous routes of exposure. In the pulmonary and intravenous injection infectivity studies, a pattern of clearance was established. *Bacillus amyloliquefaciens* strain MBI 600 Technical is minimally irritating to the skin and eyes. Slight toxicity was observed via the pulmonary route. The active ingredient is considered to be a potential sensitizer and, therefore, the hazard statement "POTENTIAL SENSITIZER" must appear on the principal display panel of the label.

Similarly, Serifel is considered to be of low toxicity via the oral, pulmonary and dermal routes, minimally irritating to the skin and eyes, and a potential sensitizer. Therefore, the hazard statement "POTENTIAL SENSITIZER" must appear on the principal display panel of the Serifel label, and the following precautionary statement must appear on the label's secondary display panel: "May cause sensitization. Avoid contact with eyes, skin and clothing. Avoid breathing dust."

When handled according to prescribed label instructions, the potential for dermal, eye and inhalation exposure for mixer/loaders, applicators, and handlers exists, with the primary source of exposure to workers being dermal. Respiratory and dermal sensitivity could possibly develop upon repeated exposure to the product since all microorganisms, including *B. amyloliquefaciens* strain MBI 600, contain substances that are potential sensitizers. Therefore, anyone handling or applying Serifel must wear waterproof gloves, long-sleeved shirts, long pants, a NIOSH-approved dust or mist filtering respirator or mask, and shoes with socks are required to minimize exposure and protect commercial applicators, mixer/loaders, and handlers that are likely to be exposed. In addition, all unprotected workers and users are prohibited from entering treated areas where the end-use products have been applied for 4 hours or until the sprays have dried.

The health risk to the general population, including infants and children, as a result of bystander exposure and/or chronic dietary exposure is low and not of concern due to the low toxicity/pathogenicity profile for *B. amyloliquefaciens* strain MBI 600, *Bacillus amyloliquefaciens* strain MBI 600 Technical and the end-use products, Serifel. The specification of an MRL under the *Pest Control Products Act* is not required for *B. amyloliquefaciens* strain MBI 600.

7.3 Environmental Risk

The submitted non-target organism test data and the scientific rationales and supporting published scientific literature previously submitted in support of *B. amyloliquefaciens* strain MBI 600 Technical were determined to be sufficiently complete to permit a decision on registration. The field use of Serifel containing *B. amyloliquefaciens* strain MBI 600 is not expected to pose a risk to non-target organisms when the directions for use on the label are followed.

As a general precaution, the product label will prohibit aerial application or the direct application of Serifel to aquatic habitats (such as lakes, rivers, sloughs, ponds, prairie potholes, creeks, marshes, streams, reservoirs, and wetlands), estuaries and marine habitats.and the product label will alsodirect handlers to not contaminate surface water by disposal of equipment wash waters and to limit runoff from treated areas.

7.4 Value

With the registration of this new method of application for Serifel, a biological fungicide already registered in Canada, grape producers are provided with a new option for the suppression of grey mould and powdery mildew. This will be of particular value to Canadian organic producers faced with a relatively limited number of currently registered product options. Further, under low disease pressure, Serifel may reduce reliance on conventional fungicides, thereby contributing positively to disease resistance management in grape production.

The proposed use of Serifel on grapes was supported based on demonstrated efficacy and the value of the product as a useful component of integrated pest management programs on Canadian grapes.

8.0 Proposed Regulatory Decision

Health Canada's PMRA, under the authority of the *Pest Control Products Act* and Regulations, is proposing registration for the sale and use of *Bacillus amyloliquefaciens* strain MBI 600 Technical and Serifel, containing the technical grade active ingredient *Bacillus amyloliquefaciens* strain MBI 600, to suppress *Botrytis cinerea* (grey mould) and *Erysiphe necator* (powdery mildew) on grapes.

An evaluation of available scientific information found that, under the approved conditions of use, the product has value and does not present an unacceptable risk to human health or the environment.

List of Abbreviations

°C	degree(s) Celsius
µg	micrograms
ADI	acceptable daily intake
ARfD	acute reference dose
CFU	colony forming unit
cm^3	cubic centimeter
DACO	data code
DIR	Regulatory Directive
DNA	deoxyribonucleic acid
EC_{50}	effective concentration on 50% of the population
EP	end-use product
FRAC	Fungicide Resistance Action Committee
g	gram
ha	hectare(s)
kDa	kilodalton
kg	kilogram
L	litre
LC_{50}	lethal concentration 50%
LD_{50}	lethal dose 50%
LOC	level of concern
mg	milligram
mL	millilitre
MCC	maximum challenge concentration
MPCA	microbial pest control agent
MRL	maximum residue limit
NC	Not Classified
NIOSH	National Institute for Occupational Safety and Health
NOEC	no observed effect concentration
OECD	Organisation for Economic Co-operation and Development
PCPA	Pest Control Products Act
PMRA	Pest Management Regulatory Agency
PRD	Proposed Registration Decision
RD	Registration Decision
RQ	risk quotient
rRNA	ribosomal ribonucleic acid
TGAI	technical grade active ingredient
TSMP	Toxic Substances Management Policy

Appendix I Tables and Figures

Table 1 Toxicity of *Bacillus amyloliquefaciens* strain MBI 600 Technical to Non-Target Species

Organism	Exposure	Significant Effect, Comments	Reference
Terrestrial Organisms			
Invertebrates			
Arthropods			
Honeybees (*Apis mellifera*), adult worker	48-hour – Contact exposure (young adult worker)	No treatment related signs of toxicity were noted in the test group. The 48-hour contact LC_{50} was > 100 µg/bee (4.4×10^8 CFU/bee). **LOW TOXICITY**	PMRA 2740090
Aquatic Organisms			
Invertebrates			
Daphnids (*Daphnia magna*)	48-hour – Aquatic exposure (static conditions)	Ninety percent of daphnids it the test group were mobile at 48 hours. The 48-hour EC_{50} was > 100mg/L (1.08×10^8 viable spores/mL). **LOW TOXICITY**	PMRA 2740091
Plants			
Aquatic Plants	72-hour – Aquatic exposure	There were no treatment related effects observed. The 72-hour EC_{50} was > 100 mg/L (5.8×10^8 CFU/mL). **LOW TOXICITY**	PMRA 2740092

Table 2 Registered Alternatives based on mode of action (as of July 2017)

Crop	Pest	FRAC Mode of Action Group No.
Grapes	Grey mould (botrytis)	2; 7; 9; 11; 17; 44; 7 + 11; 7 + 9; 9; 9 + 3; 9 + 12; NC*
	Powdery mildew	3; 5; 7; 11; 13; 44; 7 + 4; 7 + 9; 7 + 11; 9 + 3; M; U8; NC*

*Not classified biological or otherwise non-conventional fungicides

Table 3 List of Supported Uses

Suppression of botrytis grey mould (*Botrytis cinerea*) on grapes under conditions of low to moderate disease pressure / 0.25–0.5 kg/ha; repeat on 5–10 day intervals
Suppression of powdery mildew (*Erysiphe necator*) on grapes under conditions of low to moderate disease pressure / 0.25–0.5 kg/ha; repeat on 5–10 day intervals

References

A. List of Studies/Information Submitted by Registrant

PMRA Document Number	References
1.0	**Chemistry**
2740088	2016, Product Characterization Table, *Bacillus amyloliquefaciens*, Strain MBI 600 Technical, DACO: M2.1, M2.2, M2.3, M2.4, M2.5, M2.6
2740110	2017, Product Characterization Table Serifel, DACO: M2.1, M2.2, M2.3, M2.4, M2.5, M2.6
2740114	2017, Petition to register Serifel for foliar use on grape, DACO: M10.1, M10.3.1, M10.3.2, M10.4.1, M10.4.2, M10.4.3, M10.4.4
2684945	2016, *Bacillus amyloliquefaciens* strain MBI 600 Technical Group a Product Analysis, DACO: M2.10.2, M2.8, M2.9.2 CBI
2581437	2012, Genetic characterization of strain MBI600, DACO: M2.7.1
2581441	2011, Distinct differentiation of closely related species of *Bacillus subtilis* group with industrial importance, DACO: M2.7.1
2.0	**Human and Animal Health**
1951569	2010, Waiver Request - Acute Dermal Toxicity, DACO: M4.4
1951570	2010, Waiver Request - Dermal Irritation Study, DACO: M4.5.2
3.0	**Environment**
2740089	2017, Summary of Environmental Toxicity Testing with *Bacillus amyloliquefaciens* strain MBI 600, DACO: M9.1
2740090	2013, *Bacillus amyloliquefaciens* strain MBI600 Honey Bee Acute Contact Toxicity Limit Test, DACO: M9.5.1
2740091	2013, *Bacillus amyloliquefaciens* strain MBI600 Daphnia magna 48-Hour Acute Toxicity Test, DACO: M9.5.2
2740092	2013, *Bacillus amyloliquefaciens* strain MBI600 Pseudokirchneriella subcapitata 72-Hour Algal Inhibition Test, DACO: M9.8.2
4.0	**Value**
2740115	2017, Field studies in support of the petition to register Serifel for foliar use on grape, DACO: M10.2.2
2740116	2017, Field studies in support of the petition to register Serifel for foliar use on grape - Trial reports, DACO: M10.2.2
2740117	2017, Field studies in support of the petition to register Serifel for foliar use on grape - Efficacy data, DACO: M10.2.2
2740114	2017, Petition to register Serifel for foliar use on grape, DACO: M10.3.2, M10.4.2, M10.4.4, M10.3.1, M10.1, M10.4.3, M10.4.1